Section for the Study of Disease in Children.

President—Mr. J. P. Lockhart-Mummery, F.R.C.S.

DISCUSSION ON THE IMPORTANCE OF ACCESSORY FOOD FACTORS (VITAMINES) IN THE FEEDING OF INFANTS.[1]

Dr. Edward Mellanby.

It is obviously a matter of great difficulty for a laboratory worker to open a discussion concerned with the feeding of children. The task is not rendered easier by my consciousness of the exceptional difficulty in arguing from one species of animal to another when dealing with questions of diet and metabolism. Every worker on the subject of vitamines has this difficulty always before him. We must also recognize that much of the accessory food factor story has not been extended to children or tried beyond the laboratory walls. It is just for these reasons, however, that a discussion of the type we are having to-day should be of great value; because the laboratory worker and the clinician meet face to face. Each can describe his observations. The physiologist may throw new light on the points under discussion, and, still more important, the clinician may assist the investigator in evaluating his experimental results and so prevent the exaggeration of one fact at the expense of another.

We are fortunate in having the clinical side of the subject represented by Dr. Barton, Dr. Hutchison, and Dr. Pritchard. I trust I am voicing the opinions of all present when I express the wish that, not only will these gentlemen place before us the chief conditions affecting the so-called deficiency diseases, as met with in practice, but that they

[1] At a meeting of the Section, held February 27, 1920.

will also emphasize the points where it is clear the laboratory worker is going astray. Candid criticism can only do good when it is honest and based on accurate observation.

The laboratory is represented in the discussion by Dr. C. J. Martin and Professor Noël Paton. The experience of Dr. Martin, as Director of the Lister Institute, has been great as regards the accessory food factors. He has been in close touch with the work of Funk and Cooper, and in more recent years, with that of Miss Chick and Professor Harden and their colleagues. He will no doubt add his valuable experiences and conclusions to the discussion. Professor Noël Paton has not, I believe, made up his mind as to the reality of vitamines in general and my own work in particular. He will, no doubt, warn us against adopting an uncritical belief in the researches centring round deficiency disease. The statistical investigation undertaken in Glasgow by Miss Ferguson, under his auspices, has led to the conclusion that the dietetic aspect of the rickets problem is hardly worth further consideration—at least the fat content of the diet is of no importance. The Glasgow work indicates that if all children were brought up in large airy rooms instead of their slum dwellings, then rickets would disappear.

I propose to say but very few words in general introduction because most of you are no doubt familiar with the subject to some extent. In any case, it is now possible to read a general survey of the work in the book recently published by the Medical Research Committee. No doubt, the opener of a discussion ought to skim lightly over the whole subject, expound and philosophize thereon. I crave your forgiveness if, instead of doing the proper thing, I spend my time in dealing with one or two aspects of the problem which have interested me personally and leave to the other gentlemen taking part in the discussion the consideration of other portions which I shall only touch upon.

To-day we have to consider the part played in the nutrition of infants by the three known accessory food factors: (1) Antiscorbutic; (2) fat-soluble A; (3) water-soluble B or antineuritic.

From the point of view of the children of this country we can probably eliminate the water-soluble B factor. Although infantile beri-beri exists in rice eating countries and probably in other places where one-sided and limited diets are in use, the extensive distribution of this factor in food, together with its well recognized resistance to heat, would appear to make disease due to its deficiency small in western countries.

Of the antiscorbutic factor I shall say but little, and this without

authority or first hand knowledge of the subject. Dr. C. J. Martin will probably deal with this element of the normal diet. I suggest, however, that there are certain points in connexion with this factor which urgently require consideration. It would be, for instance, interesting if we could have authoritative statements on the following points:—

(1) Is the scurvy problem among children of this country one involving real danger? We know that the classical scurvy symptoms are rare, but it is not equally certain that milder symptoms indicating a deficiency short of the production of scurvy are not common.

(2) Is it essential that children feeding on dry milk compounds should take orange or swede juice?

The second problem involves an answer to two questions: (1) How much of the antiscorbutic factor is destroyed in the drying of milk? (2) How susceptible is the child as compared with experimental animals? Speaking without any particular knowledge on this point, I should think it probable that, although an infant feeding entirely on whole dried milk may not require extra antiscorbutic, yet when cereals are added to the diet, the antiscorbutic factor will be essential.

In opening this discussion, I propose with your permission to occupy the time at my disposal in dealing with what is possibly the fat-soluble A accessory factor. This I shall do for the following reasons: (1) It is the one with which I am most acquainted; (2) it is the factor which is probably most intimately related to disease in infants; (3) the discussion will largely centre about its action.

You may remember that the identification of the fat-soluble factor depended on work by McCollum in which the growth of rats was studied. The antirachitic factor on the other hand, has been so-called because of the effect of certain substances in preventing the development of rickets in dogs. Whether they are identical is unsettled, but one point of difference is so striking that it is essential to bear it in mind.

This is, that the fat-soluble factor is, according to the rat-feeding experiments, absent from all vegetable fats. In the rickets experiments, however, it seems definite that the amount of antirachitic factor is fairly high in some vegetable fats, such, for instance, as peanut, cotton-seed and coco-nut oils, and only to a small extent in palm kernel, linseed, and babassu oils.

A second point worthy of emphasis is that fat soluble A does not appear to be as necessary for growth in the case of puppies as it is in rats. It is true that all the diets of the puppies must have contained a trace of fat-soluble A, but the growth was often just as great when

the diet was very deficient in this factor as when containing it in abundance. This fact, previously described by me, has been extended to children recently by Hess and Unger. On a diet of dried separated milk, sugar, cotton-seed oil and cereal, sustained over many months, they found the growth of children practically normal. The question arises as to whether, in speaking of the fat-soluble factor in relation to child nutrition, we should still continue to call it a "growth factor." For the growth of puppies and children its influence is probably smaller than that of the other elements of the diet.

It seems most likely that both of the above described differences, viz., (1) the difference in distribution of the fat-soluble factor and the antirachitic accessory factor in vegetable fats; (2) the importance of the fat-soluble factor for the growth of rats and its probable unimportance for growth *per se* in puppies and children, can be explained by variation in the general and intermediate metabolism of these animals. These points will no doubt ultimately be solved by further experimental work. In the meantime, I would beg those who are extending the results of experimental research on rickets to children not to mix up the two types of work, namely, the growth experiments on rats and the rickets experiments on puppies. In giving cotton-seed oil to children, as recently carried out by Hess and Unger, they had in their minds undoubtedly the generally accepted fact that this oil contained no fat-soluble A. On the other hand, so far as my experiments have shown, cotton-seed oil is to be classed as one of the better vegetable oils in preventing rickets and, taken in conjunction with the other conditions of diet as described by Hess and Unger, it does not appear to me surprising that rachitic symptoms did not develop. I shall touch again on their experiments later.

From my earlier work, a short account of which has been already published, I consider that it is undoubted that something of the nature of a vitamine distributed in varying quantities in fats, plays an important part in the development of rickets. I do not wish this afternoon to deal further with this particular point. In view, however, of the erroneous and exaggerated views that are now widespread as to the action of the antirachitic factor in diet, it is essential that an effort should be made to bring such substances away from their atmosphere of mysticism, and place them side by side with other elements of the diet. If we can in some way link up their action with the known dietetic substances, so that we can discuss them in terms that are familiar, good progress will have been made along these lines. I propose, therefore, in

the remaining time at my disposal, to describe some of the more recent results of my experimental work carried out with this end in view.

The Relation of the Antirachitic Factor to Age.

It is a well-recognized clinical fact that active rickets is a rare disease in children over 2 years of age. On the other hand, arguing on the basis of my experimental results obtained with puppies, it is equally certain that, after this age, the diet of a child is often of a more rickets-producing nature, that is to say, it is frequently composed more of bread and other cereals and less of milk. The only deduction that is possible from these facts is that, after a time, a child becomes more independent of its diet from the rickets point of view. I wish to emphasize that it is only the rickets point of view I am discussing; no deduction from these results can be made as regards resistance to infection or any other pathological condition produced by diet and more particularly the anti-rachitic factor of diet at various ages. The above fact—namely, that the antirachitic accessory factor is of less importance in the older child is also brought out strikingly in puppies. It is obvious from certain well-defined facts such as the following:—

(1) After the puppy has arrived at a certain age I have been unable to produce rickets by feeding it on rickets-producing diets.

(2) On definite diets puppies develop rickets, but, if not too severe and the general condition does not become too bad, recovery at the growing ends of the bones, as indicated by radiographic examination, often takes place, although the animal may remain on the same diet and under the same conditions.

To take the first of these facts, fig. 1 is a photograph of a puppy taken when $10\frac{1}{2}$ months old. It was put on to a rickets-producing diet of separated milk, white bread, meat, orange juice and linseed oil at the age of 5 months, so that the dieting had lasted over a period of five and a half months at the time of the photograph. As a matter of fact, the dieting has now continued over eleven months, and the dog is still well and healthy and shows no signs of rickets. The radiographs seen in figs. 2 and 3 were taken of its wrist joints at the beginning and after five months of the diet. It is obvious that there is no indication of rickets having developed during this period.

The earlier treatment of this particular dog I shall refer to later, when I deal with the effect of exercise and confinement on the development of rickets.

As regards the second of the above facts, I shall now show you an instance of self-cure in a puppy when the diet and conditions were kept, as far as possible, the same as when the rickets developed. Figs. 4, 5 and 6 (p. 64) represent the changes taking place in the wrist of a puppy. The diet in this case consisted of separated milk, bread, orange juice, yeast, meat and linseed oil, and you will see that on March 28, after three and a half months of this diet, rickets had developed. It will be seen, however, from fig. 5, that one month after the first radiograph the healing process had started, and renewed calcification is evident between the epiphyses and diaphyses of the distal ends of radius and tibia. In

Fig. 1.

Puppy after three months' (second to fifth month of life) lack of exercise and living on a diet containing abundant antirachitic factor.

fig. 6 the healing process had continued to a further stage. Here, then, we have evidence of a self-curative process taking place in puppies as they grow older quite comparable to the self-cure which is well-recognized as taking place in children.

The above facts can be taken as evidence that the antirachitic accessory factor is more necessary in the diet the younger the animal, that is to say, until some essential process or secretion has developed in the young animal. Until this process has evolved, and of what its nature consists I have no idea at the present time, rickets will more readily

develop. After the necessary establishment of the new process in the young—animal or child—it is a matter of some difficulty to produce rickets. Whether all new calcification processes proceed normally after this event, even in the presence of deficient diets, still remains unknown, but further experiments will soon clear up this point. I should expect that a deficient diet will continue to act in a

FIG. 2.

Radiograph of wrist-joint of puppy in fig. 1 after three months' confinement on a full diet and prior to five months' rickets-producing diet. The joint is normal.

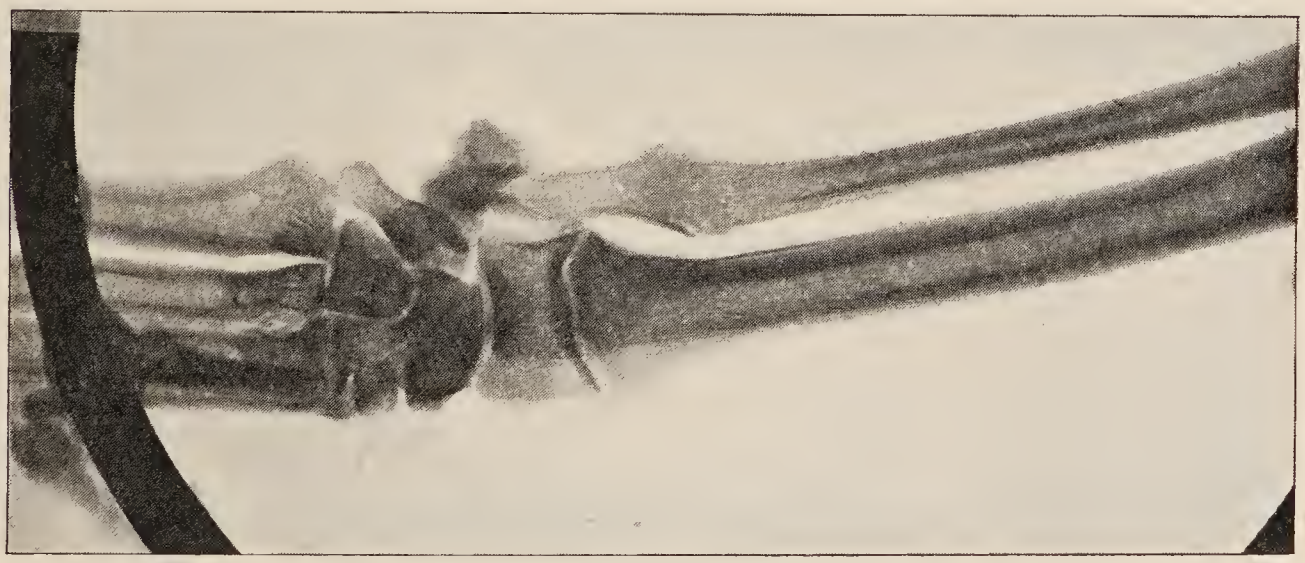

FIG. 3.

Radiograph of puppy (ten months old) in fig. 1 after five months of rickets-producing diet. The bones are normal.

manner detrimental to calcification processes, but possibly not to such a profound extent as in the younger animal and child. It is possible that the legs will continue to bend owing to poor calcification of the periosteal bone of the shafts, even after there is good evidence of a

FIG. 4.

Wrist-joint of puppy after three months' rickets-producing diet with freedom for exercise. Bones rachitic.

FIG. 5.

Later radiograph of puppy of fig. 4. Healing process started; diet and exercise continuing as before.

FIG. 6.

Wrist-joint of puppy of figs. 4 and 5. Self-curative process further advanced.

healing process going on at the epiphyseal ends. The recovery of calcification of the periosteal bone of the shaft appears to be a much slower process than that at the growing ends.

The Relation of the Antirachitic Accessory Factor to the Energy-bearing Portions of Diet.

In a paper already published I laid stress on the fact that, although rickets is primarily a deficiency disease of a dietetic nature, other metabolic conditions must obviously be involved because it is impossible to regard the accessory food factors as independent of the general metabolism and of the other elements of the diet. I emphasized the unity of a perfect diet, because we are becoming more and more aware that the removal or deficiency of one element in the diet involves much more than the absence of function or defective function carried out by this one element. It also means that the other parts of the diet cannot do their tasks efficiently because of the constant interplay between the chemical changes in the body and their dependence on each other. During the past eighteen months I have been endeavouring to prove that the same dependence and interrelationship holds between the vitamines and the proteins, fats and carbohydrates and, although this part of the work is still in progress, sufficient evidence has been obtained to allow the conclusion that their interaction in metabolism is of great importance so far as the development of rickets is concerned. I have explained in my earlier work how the tendency to rickets is increased by more rapid growth, using the weight of the animal as the indication of growth. I am fully aware that increase in weight is not a true indication of rate of growth because it obviously includes other factors, such as the laying on of fat. For the present, however, I shall confine myself to the relation of the development of rickets to the increase of weight. In many of the experiments the only variable part of the diet was bread, given generally to the animals *ad lib.* Therefore it is evident that, other things being equal, the greater the amount of bread eaten, the greater will be the tendency to rickets. This generality is probably true, so long as the increased bread intake results in an increased *storage* of foodstuff retained by the animal as body tissue. The same condition probably holds with oatmeal and other cereals.

In order to illustrate this point I shall show you an experiment carried out on three puppies of the same litter. The diet in each case

consisted of separated milk, white bread, orange juice, meat and palm kernel oil. In fig. 7 you see the relative rates of growth of these animals. In the curve of growth of 221, the least rapidly growing gained 1,700 grm., 223 gained 2,150 grm., and 220, the most rapidly growing, 2,830 grm. during the same period of sixty-six days. Throughout the experiment, except that the meat was raised from 5 to 10 grm. *per diem* a few days earlier in 220 than 223 and 221, the only variable was the amount of bread eaten. All other conditions as to housing were

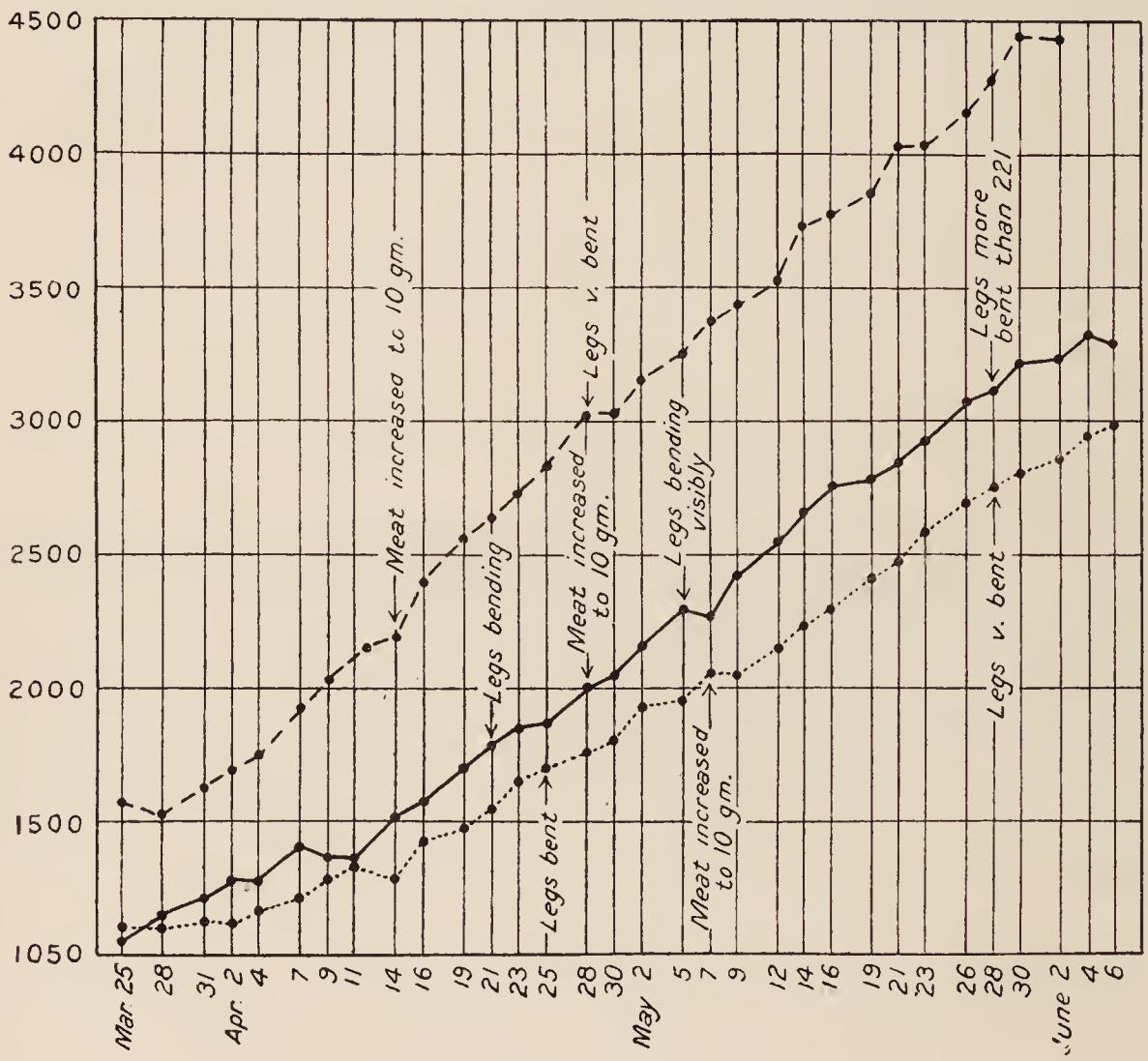

FIG. 7.

Relative rates of growth of puppies 220, 221, and 223. 220 has grown most rapidly, 221 least rapidly.

identical. If therefore any great difference regarding the development of rickets occurred, it can probably be ascribed to the variable bread intake. The radiographs of these three puppies can be seen in figs. 8, 9 and 10. It will be noticed that 221, the least rapidly growing, has very slight rickets, 220, the most rapidly growing, very severe rachitic changes, and intermediate between these two is 223, whose rate of growth is also midway between 221 and 220. Figs. 11, 12 and 13 are photographs of these three puppies, 221, 223 and 220. It will be seen

FIG. 8.

Wrist-joint of least rapidly growing puppy (221) of same family as figs. 8 and 9. Photograph of this puppy is seen in fig. 11 (p. 69). Rickets very slight.

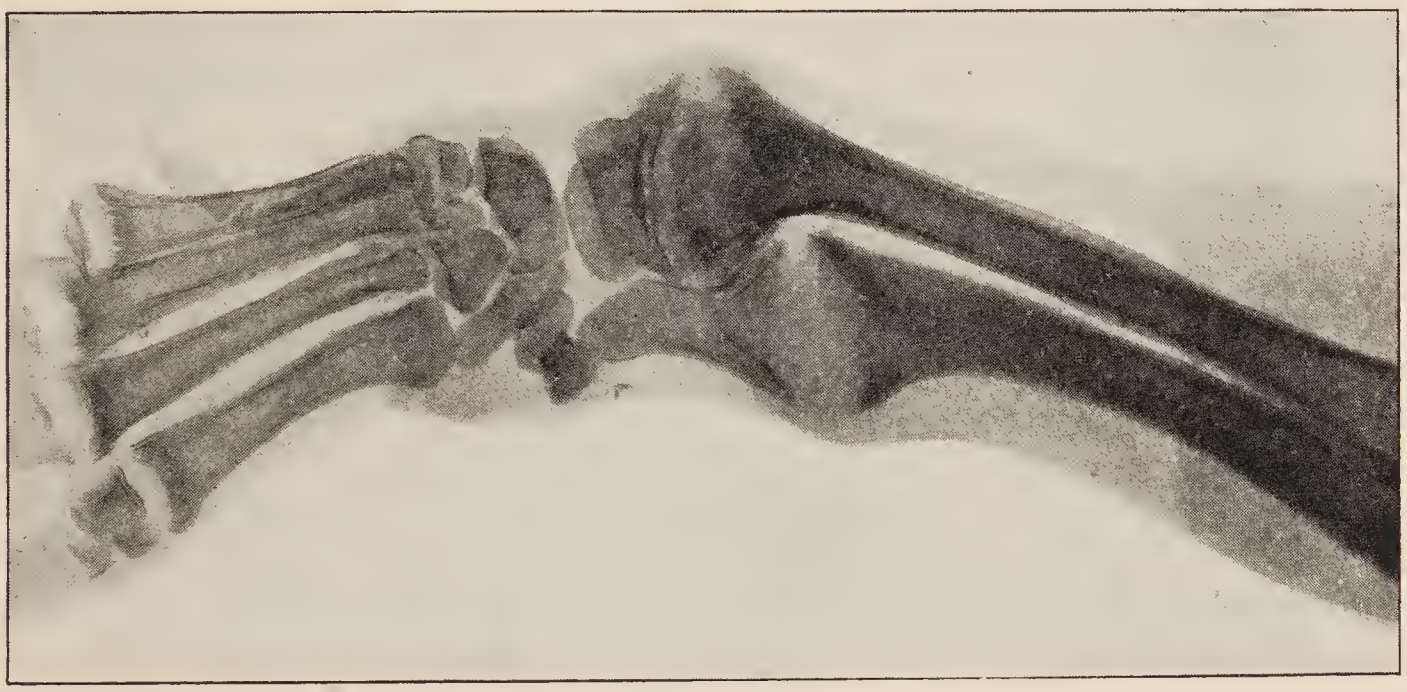

FIG. 9.

Wrist-joint of puppy 223. Rickets fairly bad. Photograph of this puppy is seen in fig. 12 (p. 69).

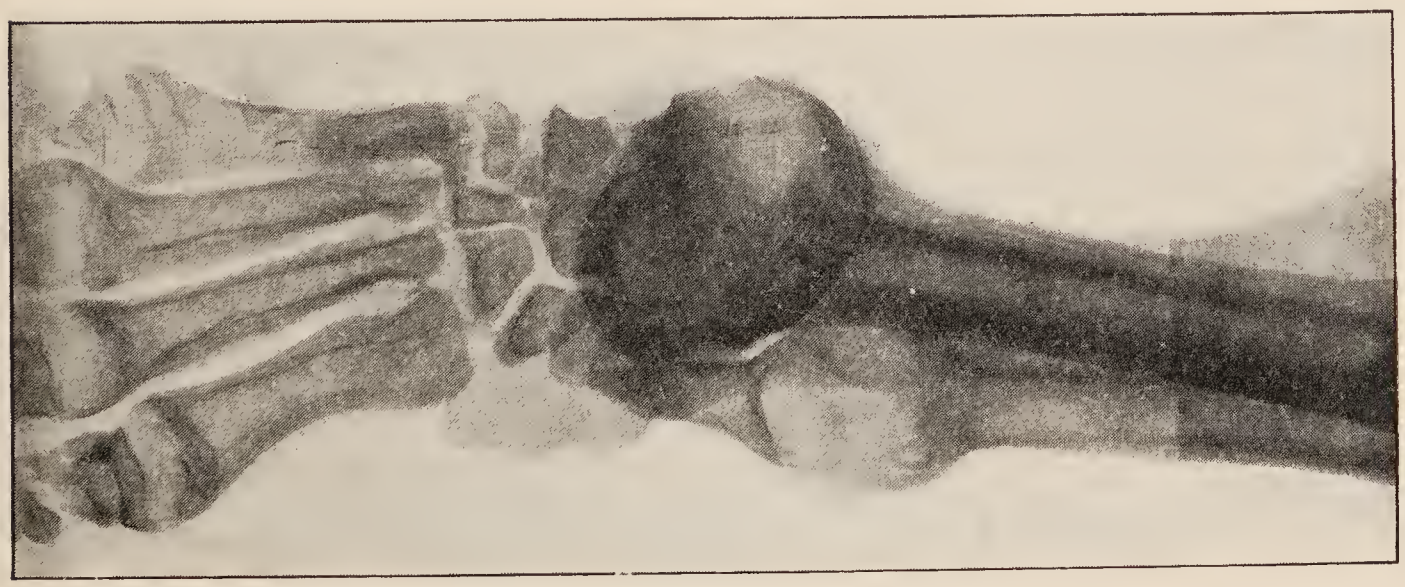

FIG. 10.

Wrist-joint of puppy 220. Rickets very bad. Photograph of this dog is seen in fig. 13 (p. 69).

that the bending and external appearances of their legs are in keeping with the radiographs of figs. 8, 9 and 10. Let me again repeat that I am only using the word growth in the sense of putting on weight. It appears then that puppies living under similar conditions show a greater tendency to develop rickets when the diet contains a larger amount of cereal, all other elements of the diet being kept constant. The question arises as to what special element of the bread is responsible for this greater tendency to rickets. This point awaits complete solution, but evidence is accumulating which indicates that the carbohydrate moiety is the offending substance. There is some evidence, on the other hand, that protein has an antagonistic action to the development of rickets. In my earlier paper, I referred to the effect of meat in making a slightly rickets-producing diet into a safe one. There is also an indication that casein has the same effect. I have been recently informed by Professor F. G. Hopkins that ordinary commercial casein, as used in these experiments, may have a large amount of the fat-soluble A accessory factor associated with it. Whether, therefore, the protein effect depends on its own action remains to be decided. If the antirachitic effect of casein is established, we will be able to comprehend one reason why milk is a better preventative of rickets than the corresponding amount of butter. I wish to make it clear that increasing the protein alone does not make a safe diet. My view is that it aids the antirachitic vitamine so that less of the latter will suffice to keep the growth normal; carbohydrate, on the contrary, especially when it results in storage of fat or makes the animal "seedy" or lethargic, appears to have a decidedly rickets-producing effect, and thereby makes additional antirachitic vitamine imperative.

It is possible that Hess and Unger's recent feeding experiments on children referred to above, in which they found that 180 grm. of a dried, separated milk powder, 30 c.c. of cotton-seed oil, 3 grm. of sucrose, 15 c.c. orange juice and 30 c.c. autolysed yeast and, later, wheat cereal *per diem*, did not produce rickets, may have, as one part of the explanation, the high protein intake of these children. I have already explained that cotton-seed oil is one of the better vegetable oils as regards its antirachitic action in puppies. 180 grm. of a dried separated milk powder must have contained about 65 grm. of protein, an amount which is abnormally high for children from 5 to 9 months old. This high protein intake, together with the antirachitic accessory factor of the cotton-seed oil, appears to me to explain satisfactorily the fact that rickets did not develop in these children. As regards their observation

FIG. 11.

Puppy 221. Very slight rickets seen in radiograph, fig. 8 (p. 67).

FIG. 12.

Puppy 223. Rachitic changes in bones seen in fig. 9 (p. 67).

FIG. 13.

Puppy 220. Very bad rickets seen in radiograph, fig. 10 (p. 67).

that the children grew fairly well in spite of the great deficiency of the fat-soluble accessory factor, this is additional evidence that it is not impossible to argue from my experimental results on puppies to children, as I have previously commented on the good growth that can be obtained in puppies in spite of great deficiency of the fat-soluble accessory factor.

I should further like to point out that the whole subject of the relationship of accessory food factors to the energy-bearing portion of the diet is one of great importance, and it is necessary that investigations on scurvy and beri-beri should also be undertaken in this connexion. It will be generally agreed that neither scurvy, nor beri-beri, nor rickets will develop as the result of starvation only. Therefore we must consider whether there is not a positive side also to these dietetic diseases. We know that in the case of scurvy and beri-beri administration of the suitable vitamine will effect a cure, but is it not also probable that the disease is brought on by some other element of the diet, since it does not develop as the result of starvation? There is some direct evidence that this is the case in avian polyneuritis, and the offending element in the diet is probably carbohydrate. Results tending to prove this have been obtained by Abderhalden, Braddon and Cooper and Funk. So, also, in the case of rickets in children, it may ultimately be established that it is excess of carbohydrate in an unbalanced diet which is largely responsible for the development of the disease. The fact that the laboratory results obtained on deficiency disease have not been entirely confirmed in practice may be the result of the omission to link up accessory food factors with carbohydrates and the other energy-bearing substances in the diet.

The Effect of Exercise on the Development of Rickets.

I have previously pointed out that, although I considered Findlay's results showing the effect of exercise on rickets to be important, yet I do not think exercise the prime factor in the ætiology of rickets but only subsidiary to diet. It is, however, obvious that the ultimate explanation of rickets must also embrace it. Whatever inhibitory effect the constant running about has in the case of puppies, we must, when considering the disease in children, discount a large part of this effect, for rickets develops in many children when only 6 months to 1 year old, and it is difficult to see how running about can play a large part at this age. The exercise obtained by children at this period

of their life consists of small movements which make up their general liveliness, and I think it will be agreed that the activity of a child depends more than anything else on the adequacy of its diet. Surely the size and number of rooms in the house where the child may carry on its movements is of subsidiary importance to its diet. If exercise and muscular contractions constitute the explanation of the ætiology of rickets, then there is clearly a simple method of eliminating the disease from Vienna, and the apostles of this gospel ought now to be preaching the glad tidings and observing its effect there. It seems to me absurd to think that the widespread and intense nature of rickets in Vienna and elsewhere in recent times has arisen primarily because of any lack of exercise or because of the more defective hygienic conditions that may have developed within the last few years.

My experiments on exercise have been made along various lines and the results obtained may be briefly stated thus:—

(1) Confinement on an adequate diet will not produce rickets.

(2) Freedom in the daytime will not prevent rickets when the diet is inadequate.

(3) Confinement will not prevent the cure of rickets, so far as the growing ends of the bones are concerned, when the diet is good.

On the other hand, complete freedom and the possibility of constant running about will oppose to some extent the rickets-producing effect of a deficient diet and may carry it over to the safe side in small slowly-growing dogs.

Fig. 1 (p. 62), which is a photograph of a dog I have previously referred to, was confined from the second to the fifth month of its life. Its diet consisted during this period of 250 c.c. whole milk, 20 grm. meat, 5 to 10 c.c. cod-liver oil, 5 c.c. orange juice and white bread. In spite of the absence of the opportunity for exercise it was a beautiful dog, showing no signs of rickets, as can be seen from the radiograph, fig. 2 (p. 63), taken after the period of confinement.

The brother of this puppy was allowed complete freedom during the daytime (with a special type of muzzle on) and developed slight rickets, which can be seen in fig. 4 (p. 64). It was eating a rickets-producing diet during this period consisting of 175 to 250 c.c. separated milk, white bread *ad lib.*, 5 to 10 grm. meat, 10 c.c. linseed oil and 5 c.c. orange juice. This animal was an instance of self cure and, while living under the same conditions, calcification of the growing ends of the bones was resumed. This point is seen in the radiographs (figs. 5 and 6, p. 64), and has been previously commented on. The rate of growth

of 199 was not very good: it increased 2,730 grm. in nineteen weeks while eating the diet.

Here, then, we have instances of two puppies (terriers) and members of the same family, the one remaining normal in spite of lack of exercise and the other developing rickets with full opportunity for exercise. The dominant factor in each case was the diet. The first dog had an abundance of antirachitic factor in its diet, which included whole milk and cod-liver oil. The second on separated milk and linseed oil was getting little or no antirachitic factor. I wish to repeat, however, that muscular contraction has some inhibitory action in the development of rickets and must be considered in the general scheme.

The points I have discussed to-day, more particularly the relation of the antirachitic accessory factor to the energy-bearing portions of the diet and to exercise, indicate plainly that rickets must be considered as a problem of general metabolism. As a working hypothesis it seems possible to formulate a general scheme in which each of the various elements already discussed can find a place. Any condition which induces a laying on of tissue seems to necessitate a greater intake of antirachitic accessory factor to prevent rickets. On the other hand, conditions which stimulate the metabolism and increase the heat loss relatively to the energy of the stored food work together with the antirachitic accessory factor and make a less amount necessary for normal growth. For instance, excessive carbohydrates in the diet often brings about a condition of laying on of fat associated with lethargy. The diet under these conditions must have much antirachitic accessory factor, otherwise rickets develops. Proteins and exercise are stimulants to the metabolism and, when the diet has a relatively good protein content and the animal is active, less antirachitic accessory factor is necessary.

It is upon this hypothesis that my present investigations on rickets are being continued, and, while it is freely admitted that it is not based on complete experimental evidence, a general conception is always useful to an investigator and can do no harm so long as it is regarded by others in its true light. The generalization may not explain all conditions under which rickets develops, but we are in the satisfactory position of knowing that its proof or disproof can easily be tested by further experiment.

The Importance of the Antirachitic Accessory Factor in the Feeding of Children.

Up to the present I have dealt entirely with the effect of the antirachitic vitamine in the case of puppies, and I think you would probably find it interesting if I attempted to supply some evidence which supported the animal results and showed that, in the case of children also, this substance is of great importance. I shall deal with two investigations[1] carried out at a time when the presence of the antirachitic accessory factor in food was undreamt of.

In examining school children at Leeds, Dr. William Hall was much interested in the great difference in general nutrition, and more especially in the teeth of Jewish and Gentile children, the financial position and housing of whose families were comparable. The results of his investigations were described at a Health Congress in Leeds in 1902, and his general observations and conclusions are so concordant with my experimental results that I should like to record them. The following table represents a few of these results :—

		Rickets		Bad or backward teeth
Good district	Gentile school ...	8 per cent.	...	38 per cent.
,, ,,	Jewish ,, ...	5 ,,	...	11 ,,
Poor ,,	Gentile ,, ...	50 ,,	...	60 ,,
,, ,,	Jewish ,, ...	7 ,,	...	25 ,,
Country school (Ripon Cathedral School)	... ...	11 ,,	...	33 ,,

The great difference between these two classes of people, more especially in the poor schools, is very striking. It will be further observed that the condition of the poorest Jewish children is better than that of the country children.

Hall then proceeded to investigate the cause of the above described differences and finally decided that only the dieting could be held responsible. From his analysis of the diets, which he found very different in the two classes of the community examined, I take the following points :—

(1) The Jewish families used large quantities of oil in cooking—even in making bread. Fish were generally fried in oil. Potatoes were not boiled in water; if boiled, it was usually in milk; otherwise cooked in oil. In making broth, butter and oil were added to it.

[1] These instances were kindly brought to my notice by Dr. Scurfield, Medical Officer of Health for Sheffield.

(2) The normal beverage was cocoa made with milk. This was usually drunk three times a day, except on the days when meat was eaten.

(3) An analysis of the eggs eaten by the Jewish families showed the large number consumed.

(4) Fruit and vegetables were used abundantly.

(5) The Jewish mothers combined to buy large quantities of the cheaper fish in the market. Herrings were commonly eaten.

Dr. Hall's conclusions as to the inferior physique of the Gentile families were: (1) That it did not depend on heredity or on city life; (2) that it was purely a dietetic problem.

My researches on animals are in complete agreement with the outcome of these investigations. The diet is certainly the key to the physical defects so common among urban and city inhabitants. It is also remarkable how closely the diets of the Jewish community, as observed by Hall, follow the animal experimental results. Nearly all the substances mentioned by Hall contain an abundance of antirachitic accessory factor.

The next subject connected with diet and child nutrition to which I wish to refer concerns the inhabitants of the Island of Lewis in the Hebrides. The facts I shall mention are taken from the Carnegie Report of the Physical Welfare of Mothers and Children of Scotland. Many of the inhabitants of these islands live in what are called "Black Houses." A photograph of a typical "Black House" is shown in fig. 14. They are constructed of turf and stones with a thatched roof. There is often no chimney to the house, and since the peat fires are kept constantly burning and there is no exit for smoke, except through the door, the condition of the atmosphere of the house can be well imagined. The walls are often as much as 5 ft. thick. Cattle often live under the same roof, the byre adjoining the house, and it is sometimes necessary to pass through the byre to enter or leave the building. The chicken have full run of the house and go on to the beds, tables and dressers. Altogether the hygienic conditions are dreadful. What about the children? The statements are made in the report: "The children are not taken out until they can walk;" "never taken out till they can walk, except possibly for a few minutes on a fine day in the summer time." It is quite clear, therefore, that, if bad hygiene and lack of exercise are responsible for rickets and ill-health, then the infants of Lewis ought to succumb at a great rate.

What are the facts? The main fact is that the death-rate of these

infants under 1 year is about the lowest in the British Isles, and has occasionally fallen to as low a figure as 40 per 1,000. This death-rate compares very favourably with the infantile mortality of 100 to 300 per 1,000 usually found in the towns of this country, in spite of the efforts made to improve the general hygiene. It is remarked that rickets is almost unknown in the island, and the most striking feature in the adult population is their beautiful teeth—a testimony to the absence of rickets in infancy. Parenthetically, I regret that lack of time has prevented me from showing on the lantern some of the beautiful specimens of my wife's work on teeth—work that has shown that the formation of perfect and imperfect teeth and jaws is affected by diet in a similar way to the development of the normal and rachitic condition of bones.

FIG. 14.

A typical "Black house" in Lewis (Hebrides) where the teeth of the people are excellent and there is no rickets, in spite of bad hygienic conditions.

If we now examine the diet of these people we find results in close agreement with expectations based on the above described experimental work on puppies. In the first place practically all the children are breast fed. Again an analysis of the foods eaten show that the staple articles of diet are fish, oatmeal and eggs. It is true that milk is scarce, except in the summer, but against this we have breast feeding, affording the opportunity to children to get milk at the most important period of their life. As regards fish we find that the liver (i.e., the best source of the antirachitic accessory factor) is regarded as the favourite dish. It

is described as being mixed with oatmeal and milk and cooked in cods' heads, each member of the family being provided with a cod's head. It is almost certain that the breast feeding of the children, together with the high protein and antirachitic accessory factor content of the adult diet, are responsible for the absence of rickets, the formation of beautiful teeth and the very low infant mortality found in these islands and, that this is the case, in spite of the dreadful hygienic conditions of many of the houses. For the benefit of those interested in the antiscorbutic factor, I may mention that vegetables are almost unknown in these parts. Evidence is accumulating from various sources, showing the effect of the diet of the mother on the accessory food factor content of milk, so that it is likely that the milk of the Lewis women is particularly rich in the antirachitic accessory factor. I do not wish, however, to discuss this point to-day. If we follow up the mortality and health history of the Lewis children after the age of 1 year, additional facts of importance can be observed. From 1 to 5 years the death-rate among the children is high when considered in relation to the infantile mortality under 1 year. The housing conditions are such that epidemics spread rapidly and fatally, and phthisis in 1914 caused a death-rate double that on the mainland. When the children begin to go to school, they fall off rapidly until they attain an age when they can look after themselves. This is because they generally have to go to school before their parents are out of bed, and so often do not get a real meal until midday. When the children have arrived at an age at which they can fend for themselves and satisfy their appetite by seizing food, if need be, then they develop well and ultimately become the fine stock so well recognized as coming from these islands.

I have dwelt on this particular point because it seems to afford an opportunity of realizing to some extent the relative importance of diet and housing at the different ages. It is difficult to avoid the conclusion that diet is everything to infants under 1 year, and, so long as this is good, bad hygienic conditions are of small significance. After the first year, however, when the child becomes susceptible to measles, broncho-pneumonia, and other infections, then clearly the housing and hygienic factors in addition to the diet are of great importance. If these suggestions could be definitely proved and accepted, we should have gone a long way towards the solution of the problem of race decadence. It is reasonable to accept as facts that where there is low infant mortality, there is an almost complete absence of rickets and the teeth of the people are good; also that the production of rickets depends on a

relative insufficiency in the diet of the antirachitic accessory factor, the best sources of which are fish oils, animal fats, except lard, milk, eggs and some of the vegetable fats. It is also probable that anything which stimulates metabolism, such as high protein in the diet and exercise, aids the antirachitic accessory factor; while excess of carbohydrate, especially if it leads to a laying on of fat or a production of lethargy, works in a way antagonistic to the vitamine and makes it necessary to have a greater amount in the diet to ensure normal growth of bone, formation of sound teeth and jaws, and good general health.

My investigation on rickets is still in progress and the results remain incomplete. The mode of production of the disease is obviously complex, otherwise it would have long been solved, but by considering and altering each factor in turn, the animal experimental method will certainly in time clear up all the points of difficulty.

I feel I owe you an apology for having introduced the discussion in such a one-sided way, but, if I have succeeded in increasiug your interest in a new aspect of the problem, which I hope will prove of great practical value, I shall probably have earned your forgiveness.

Professor Noël Paton, F.R.S.

It is curious and interesting that a discussion of this kind should be opened by one physiologist and followed by another. I take it as a welcome admission by the clinician that we are brethren who can and should help each other. The physiologist will always be ready to acknowledge his indebtedness to the clinician whose work and observations have suggested to him so many of his most profitable lines of work and he is, now, at least trying to repay the debt by applying some part of his time to the solution of problems of importance to the clinician—witness the investigations carried out on wound shock and gassing during the late war. In doing this I think that he must recognize that it is his duty to present for the acceptance of his clinical brother only those results which have been thoroughly tested, and that he should remember that the man in practice is just as able as he is to assess the value of the evidence presented and that he should not insult his intelligence by asking his acceptance of statements without that evidence being given. This is just what I object to in the attitude of many physiologists to the present craze for vitamines—a horrible name since we do not know that, even if they exist, they are amines, or what

they have to do with life. What we do know on the subject may very briefly be stated :—

(1) Hopkins and Willcock, and Osborne and Mendel have shown that minimal quantities of certain amino-acids are necessary for growth. They are limiting factors for growth.

(2) The same has been shown by McCollum and others for inorganic substances, chiefly calcium and phosphorus.

(3) In various animals it has been shown that the absence of some water-soluble food constituent or constituents leads to arrest of growth and death, or to the onset of scurvy or beri-beri.

(4) In rats and mice it has been shown that minimal quantities of certain fatty mixtures—e.g., of milk fat or cod-liver oil—are necessary constituents of the diet for growth. With a deficient supply of these growth is arrested in these animals. In dogs, according to Mellanby, growth is not arrested, but rickets is produced. Of their effect upon other animals we know nothing. What of kittens, piglings, chicks, and what of infants ?

On such a basis have we any right to draw any far-reaching conclusions ?

Why do not clinicians arrange a series of experiments in institutions to study the effects of these substances, instead of being satisfied with personal experience or remaining content to argue from the divergent results in rats and pups to the human subject ? I am, of course, aware that such clinical work has been done and I shall presently deal with the observations of Hess and Unger.

I do not propose to speak further upon the general question of vitamines. My work has been done on rickets and I shall confine myself to the evidence that this is a disease due to want of vitamines. In doing so, I must refer to the recently published report of the Vitamines Sub-committee of the Medical Research Committee. The part of the report which deals with rickets is certainly a request to "open your mouth and shut your eyes"—to accept statements unsupported by evidence. But what we have to do is to estimate the value of the evidence adduced. What evidence have we at present as regards the cause of rickets ?

I purposely refrain from touching upon the older work on rickets, an excellent résumé of which is given by Findlay in the introduction to Miss Ferguson's report. Von Hansemann's "domestication" may mean anything—confinement, feeding or filth, and it is needless to discuss such an abstraction.

First, we have some evidence upon the possibility of rickets being associated with abnormal conditions of the thymus. The observations of Friedleben, Von Basch, Klose and Vogt and Matti seemed to give support to this view. The experiments of Renton and Madge Robertson in this laboratory show quite clearly that rickets occurs as readily in animals with the thymus as in animals without it. They found that however well fed pups kept in a laboratory may be, there is a great tendency to the development of rickets, a tendency more marked in some breeds than in others. The recent paper by Park and McClure in the *American Journal of the Diseases of Children*, November, 1919, supports the conclusions of Renton and Robertson that rickets is not due to thymus insufficiency.

Leonard Findlay, in 1908, reviewed the existing evidence and recorded a series of experiments upon sixteen puppies which he considered proof that confinement and not diet is the determining factor in causing rickets. He found that puppies fed on bread and water simply wasted and died without developing rickets, in the same way as rats wanting the fat-soluble substance waste and die. All the puppies kept confined (eight) developed rickets; the five not confined to the same diet of porridge and milk did not do so. Mellanby criticizes the results on the supposition that Findlay gave only 175 c.c. of milk, a purely gratuitous assumption. They had an abundance of milk. He further suggests that the diet was not a healthy one because two of the pups died. It is the diet on which most of the pups in Scotland are reared. How many of Mellanby's 200 dogs died? My criticism of Findlay's experiments is that only in one case were the confined pups and the checks of the same litter and it is unjustifiable to argue from such results, obtained from different litters, since the susceptibility of different strains is different.

The report of the Vitamine Committee is avowedly based upon Mellanby's results. We can judge only of its value from the results which have been published. These appeared in the *Lancet* of March 15, 1919, pp. 407-412. He states that he cleared the way for his dietary experiments by a series of experiments to show that other factors were not operative. These experiments he does not record and we cannot estimate their value. We have thus Findlay's recorded results on the one side, and Mellanby's statement on the other, neither of which justifies any definite conclusion.

As to the influence of the dietary factors, he has recorded observations upon thirty-three pups, ten normal and thirteen which developed

rickets. Presumably the experiments selected for publication were not the least convincing of his series. When the records are examined it is found that the dogs grouped together *were not always of the same litter.* Now, to contrast animals of different litters is, as already stated, wholly unjustifiable, since the susceptibility of different strains to rickets is notoriously different. Further, in his groups the pups were not always killed at the same age, and yet the calcium content of the bones is compared, although, as everyone knows, this varies with age. The same puppy is included in different groups.

In this small series of observations no less than thirteen substances were tested and conclusions drawn as to which of these allows and which prevents rickets. In the Report of the Vitamine Committee a list of thirteen substances which do not prevent and of eleven substances which do prevent rickets is given upon page 83, with no published evidence except that of Mellanby's paper. Certainly on such a basis it is ridiculous to ask any reasonable man to accept the conclusions :—

(i) That rickets is a deficiency disease due to the absence of an accessory factor probably identical with the fat-soluble substance.

(ii) That certain specified articles of food prevent its onset while others do not prevent it.

Our observations recorded in the *British Medical Journal* of December, 1918, were made upon seventeen puppies of two litters. The main object was to get rickety pups and sound pups of the same litter for chemical examination. But a test was also afforded of the relative influence of diet and open air life. From each litter two puppies were sent to the country, kept in a large yard and fed upon oatmeal porridge and skimmed milk, so that each had 2·8 grm. of milk fat per day. Those kept in the laboratory had whole milk containing during the first period of their growth, 3 grm. of milk fat per day, and during the later period 6 grm. In addition to this, three of the puppies had butter in an amount to yield, along with the milk, 14 grm. of milk fat. The puppies kept in the country on the lower fat intake remained absolutely normal. All the puppies kept in the laboratory developed rickets, one of those receiving butter became most distinctly affected. It has been suggested that puppies kept in the country get their fat-soluble substance by eating grass. Unfortunately for this theory, the carnivorous alimentary canal does not digest grass, even when swallowed. It has further been argued that confinement may so depress digestion that the fat-soluble substance is not absorbed from the food, but there was no indication of disturbed digestion and

Mellanby has stated that confinement does not cause rickets. In the last experiment the pups were given a very large amount of oatmeal, and the energy intake was superabundant. Watson, during the present winter, has made observations upon two litters of puppies with a more limited energy supply in the food. No final conclusions can be based upon them. At the first glance they seem to support the view that milk fat has an influence in retarding the onset of rickets, but the fact that at least two of the pups on 250 c.c. of whole milk developed rickets, and the further fact that those on skim milk had an energy intake so much lower than the others, render definite conclusions impossible.

In the Vitamine Committee's report no reference is made to Bull's interesting investigations of an epidemic of rickets among foxhound puppies at Adelaide in 1912.[1] The kennel had previously been free of rickets. The epidemic, when it broke out, affected practically all the puppies. The animals had been fed on boiled meat and pollard, the only change being that before the outbreak the pollard had been substituted for wheaten meal. He found that the most potent factor in preventing and curing the condition was to remove the pups from the yard in which they had been kept. He found, for instance, that two pups, when taken away and kept upon their ordinary food, did not develop rickets. He reported that affected puppies which had a supply of milk improved most rapidly. A litter of two pups and their mother were moved to a specially prepared yard, given the same food, but remained free of rickets. His conclusion is : "It was found that almost any change in the environment or diet would at once modify the occurrence and intensity of the disease. When the animals were kept in the same yard that had been used for some years for confining the puppies, but the diet was altered, a modification was produced—namely, the disease became less severe in its manifestations and not all the animals were affected. *When removed from the kennels animals developing the disease showed improvement and sometimes complete recovery irrespective of the nature of the diet.*

"Undoubtedly the food the animals were receiving was very unsuitable and closely associated with the production of the disease, but it could not be regarded as the essential cause. *It was not until a new yard was prepared for the puppies that the occurrence of the disease was prevented, even when the old diet was continued.*

[1] *Journ. Comp. Pathol.*, xxxi, 1918.

"It would appear, therefore, that at least two conditions were associated with the occurrence of the disease—namely, environment and food. But it has been shown that the particular food used for some years at the kennels would not produce the disease when other conditions were altered. On the other hand, it was found impossible to prevent the occurrence of the disease completely when the diet only was altered, although the evidence in this regard is inconclusive; and one is inclined to believe that, had more opportunity occurred of improving the diet, the disease would probably have been completely controlled.

"In contrast with this, more or less satisfactory improvement following change of diet is the most marked success obtained by change of environment. This stands out as a positive fact, that the same diet had consistently been associated with the disease being given, the disease could not be produced in puppies, even of the same breed, when fed away from the kennels or on some other part of the property that had never been used for similar purposes before."

Some returns which I procured from the huntsmen of some of the larger hunts upon the incidence of rickets in the foxhound whelps give little support to the idea that deficiency in a fat-soluble substance is a causal factor in the onset of the condition.

TABLE.

Number of whelps	Food	Exercise	Rickets	Age of incidence	Remarks
(I) 120 to 140	Oatmeal, biscuits, meat, milk (skimmed and scalded)	Grass run, fresh ground daily	Occasional	2 to 3 months	Exercise
(II) 70 ... (Peace, 200)	No milk, ordinary kennel food	Big field	After distemper	8 to 10 months	—
(III) 40 to 60 (Peace, 170)	Oatmeal, biscuit, milk, half pint (best boiled)	Large kennel in fresh field	Yes, if kept confined or overfed	9 to 10 weeks	Get them away for liberty
(IV) 160 to 190	Food given to old hounds; do not use milk	Good large pen	Yes	All ages	Puppies sent off at 8 to 9 weeks
(V) 40 to 60 ...	Cow's milk, new, half pint	Pen, six yards square, on grass	No, except in bad mothered pups or worms	3 to 9 weeks	—

Investigations on Children.—The series of investigations which have been given the most prominence is that of Hess and Unger upon negro children in New York. According to the authors, about 90 per cent. of these develop rickets. From observations upon thirty-two children,

they state that the administration of 54 oz. of cod-liver oil for six months prevented the onset of rickets in 93 per cent. of the cases. Their Table I has been largely used by the champions of the vitamine theory, but it would have been well had they read the paper. A reference to Table III would have shown them that ten out of the thirty-three children treated had rickets before the oil was administered and that they had merely improved during the six months under oil. As a matter of fact, in the Table III, six are noted as unchanged and two progressed—became worse. This hardly justifies the statement in Table I as regards the prophylactic action of oil. Miss Ferguson, under the direction of Leonard Findlay, has repeated these observations upon sixty-two children, of from 1½ to 12 months, with cod-liver oil to about 2 oz. per week, that is about the same amount as given by Hess and Unger, was given for about six months. The cases were examined before starting treatment and were all free from rickets. They were examined again at the end of six months by Dr. Findlay, who reports: out of twenty-seven oil and thirty check cases present at the examination there were :—

	Oil	Check
Non-rachitic ...	23 = 85 per cent. ...	10 = 33 per cent.
Rachitic	3 = 11 ,, ...	18 = 60 ,,
Doubtful	1 = 4 ,, ...	2 = 7 ,,

Note on Teething.—On an average, the controls are behind those receiving oil by about one tooth a month from seven months onward.

Such an observation lends support to the view that cod-liver oil has a favourable action, but whether this is due to a vitamine or to some other action is not indicated. The investigation is still in progress.

Miss Ferguson, in 1917, undertook an investigation of the diets and social conditions of families in which rickets occurred and in which rickets had not occurred—forty-seven families in all—of the same social class in the city of Glasgow where rickets is very prevalent. She found no marked difference in the dietary habits: both sets of families used very small quantities of milk, the average in the non-rachitic families being 6·7 oz. per person per day, and in the rachitic families 4·7 oz. Of twenty-seven rachitic families, twenty—i.e., 74 per cent., and of twenty non-rachitic families, twelve—i.e., 60 per cent. had less than 30 c.c. milk, expressed as per man per day. In quite a number of the non-rachitic families the milk consumed was as small in amount as in any of the rachitic. Mellanby criticizes these results, on the ground that (1) such family studies throw no light on the feeding of the infants,

and (2) they show that in the families with rickets the children got less of "substances delaying or preventing rickets." One cannot argue in both ways.

Here let me point out that the criticism of family diets made in the report of the Sub-committee that they give the amount of the proximate principles but not the actual foods used is untrue, so far as the Glasgow studies are concerned.

Lastly, I must refer to the most recent publication by Hess and Unger on "The Clinical Rôle of the Fat-soluble Vitamine; its Relation to Rickets."[1] It is a most cogent criticism of the findings of the Vitamine Sub-committee, supported by a valuable series of observations. They show that the bone changes in scurvy may simulate those of rickets. They find that rickets develops notwithstanding an abundance of fresh air. They record a series of experiments to show that infants getting abundance of milk fat become rickety, while others kept upon a fat-poor diet remain almost free from the disease. They conclude: "It would lead too far afield to discuss the various theories that have been advanced to account for the occurrence of rickets, and, moreover, it would not be profitable at the present time as the data are inadequate. There seem to be several causes at work, rendering the unravelling of the problem so difficult that there is a difference of opinion, not only as to the particular dietary factor that is at fault, but even as to whether rickets is to be considered a disorder of dietetic origin. It should not be lost sight of that there is a pre-natal factor involved. The fact that the negro infant, living side by side with the white in the larger cities, and obtaining milk from the same source, develops rickets so frequently and so markedly, indicates that there are important influences to be reckoned with in addition to the food."

In considering the diet a most important question is whether the recent theory as to the vitamine origin of this disorder can be maintained, and more particularly whether rickets should be attributed to a lack of the fat-soluble factor. We can obtain the clearest understanding of this aspect by comparing this disease to the well-recognized and established deficiency diseases, scurvy and beri-beri. What does the comparison show? In the first place, these two disorders are commonly accompanied by weakness and malnutrition; we do not encounter the strong, apparently healthy, babies met with in

[1] *Journ. Amer. Med. Assoc.*, January 24, 1920.

rickets. But of far greater moment is the fact that neither can be brought about by overfeeding. Rickets, as I have already emphasized, frequently develops in infants receiving too much milk rich fats, protein and salts. It seems impossible to bring this fact into consonance with a deficiency disease, whatever may be its nature, using this term in the commonly accepted sense. Our study shows that the fat-soluble vitamine is not the controlling influence; that infants develop rickets while receiving a full amount of this principle, and that they do not manifest signs, although deprived of this vitamine for many months, at the most vulnerable period of their lives. It is impossible to interpret the contrary conclusion to which Mellanby came as the result of his pioneer experiments on dogs or to accept the term "fat-soluble vitamine" as synonymous with "antirachitic factor" as Hopkins and Chick would have us do. Clinical tests carried out with care must be accorded fully as much weight as laboratory investigations. The two methods of approach should be carried out side by side, and even the most thorough study on animals must be made to harmonize before it can be accepted as holding good for man.

Finally, this work seems to show that the danger to infants of a diet deficient in fat-soluble vitamine is slight, provided it includes sufficient calories, and otherwise is complete. They can maintain their health and vigour, despite amounts of fat-soluble vitamine so small as rarely to be encountered in times of peace. In spite of the fact, therefore, that this vitamine is not widely distributed in nature, a disorder that may be termed "fat-soluble deficiency—marasmus or xerophthalmia—is hardly to be apprehended from a clinical standpoint." They also state: "There is a growing danger of attributing every unexplained growth impulse to the new, attractive but ill-defined vitamines: of their sharing with the secretions of the endocrine glands the fate of becoming the dumping ground for every unidentified factor. It should be borne in mind that there are other little understood factors and food reactions."

These results are in conformity with those of von Pirquet ("System die Ernährung") that "A fat minimum does not exist for domestic animals. Fat can entirely be replaced by carbohydrates. This may happen through a lifetime where the natural nourishment, milk, affords a rich fat content; in the weaning of calves sour 'magermilch' is used, to which fat-rich seeds or cake (linseed, or linseed cake, or coco-nut cake) may be added, but also, just as well, meal or bran. I have made experiments in this direction upon sucklings in which I replaced the

usual milk mixture with an entirely centrifuged de-fatted milk, the calorie value of which was brought up to the normal by cane sugar. In spite of the fact that the fat-less diet was suddenly given without any gradual transference, no influence was noticed on the course of the weight curves of the children and only once was any influence noticed on the stools."

The periods over which these fat-less diets were given were too short to allow of conclusions being drawn as to the influence on the onset of rickets.

I agree with Hess and Unger that we are not yet in a position to discuss the ætiology of rickets until we have done a great deal more work. Certainly it has not yet been proved to be a deficiency disease due to the lack of some fat-soluble substance. Nor do I think it has been proved to be due to the lack of exercise. But it is directly correlated with overcrowding and confinement in insanitary houses. The possibility that it is primarily an infective disease has never been disproved. It might be due to non-specific micro-organisms, possibly of fæcal origin, in the same way as goitre has been shown by McCarrison to be due to such infections. Certainly the more scrupulously clean the kennels are kept, the less seems to be the tendency for pups to develop rickets. This is indicated by Bull's observations.

What we want is a combined co-ordinated study of the disease from the clinical and from the experimental side. Rickets is so prevalent and is of such enormous importance from the economic standpoint, that it is well worthy of the most serious study. In the interests of the nation, I trust that the Medical Research Committee will be able to institute such a comprehensive investigation.

Dr. Robert Hutchison.

The causation of rickets has always been a puzzle to clinicans, but up to the present the advent of the experimental pathologist in the field has only served to darken counsel. In my opinion Dr. Mellanby has certainly made out a *prima facie* case for the view that rickets is the result of the absence of some accessory substance from the diet although it does not appear to be the ordinary fat-soluble A. On the other hand Professor Noël Paton's experiments have led to an opposite conclusion, nor, apparently do rats develop rickets when fed on a diet devoid of the growth vitamine. It should further be remembered that Herter[1]

[1] *Journ. Exper. Med.*, 1893, iii, 293.

fed young pigs on a fat-free diet for prolonged periods, and although their nutrition suffered they did not develop anything even suggesting rickets. If the results of experiment differ in rats, puppies and pigs, how can we apply them to babies?

Clinical evidence is in favour of the disease being a dietetic disease, for it can be cured by altering the diet; the other factor is in the environment remaining as before. The dietetic fault is certainly not an all-round deficiency, for rickets is, perhaps, commoner in over-fed than in under-fed children. It seems rather to be caused by an ill-balanced diet and particularly by one which contains a relative excess of carbohydrates. How this causes rickets it is impossible to say, but then Dr. Mellanby is unable to say how the absence of a "vitamine" causes it either. If an accessory substance plays any part at all it must be that it is required to counteract some other defect in the diet and not merely that it supplies in itself something that is essential and without which rickets will develop, no matter what the composition of the diet is as a whole. The same is true of scurvy. Infants rarely develop scurvy on a diet of condensed milk alone, but if a starchy food were added to the condensed milk, scurvy is very apt to appear. The antiscorbutic accessory substance must in some way actively counteract the bad qualities of food and diet, and not merely supply something lacking, for it is equally lacking in the condensed milk alone. It may be necessary to assume this kind of action on the part of the accessory substances, but it is attributing to them rather a different rôle from that with which earlier investigations have credited them.

I am of opinion that as regards rickets, at least we want more evidence before calling in the action of a hypothetical accessory substance at all. It must be remembered that vitamines are the latest dietetic "stunt," and we must be careful not to push their significance too far and not to draw sweeping practical conclusions from our at present very inadequate knowledge of them.

Professor C. J. Martin, F.R.S.

I listened with the very greatest interest to Dr. Mellanby's opening of this discussion, and it struck me as not only being excellently served up, but also as being very moderate in the conclusions drawn.

Dr. Mellanby brought before you some facts, and those facts have to be explained. The importance of them to me is their orientating value. You have, ultimately, to test any interpretation of the essential

causation of rickets, whether it be in children or in animals, by studying the disease in children and in animals as it occurs. I would not wish for a moment to depreciate the value of clinical observations, or the physician's capacity for making such observations or weighing the value of the evidence. Scientific work is scientific work, whether it be done at the bedside or in the laboratory workshop. It is the method, not the material, that matters. But, in scientific procedure, one must have some idea to guide one. You may have patients and see things going on, and you may make careful observations: but you do not know what particularly to observe and record unless you have an idea as to what is happening to test.

I can add but little to the discussion on rickets, but it struck me that Professor Noël Paton's contribution was not a serious assault upon the opener's position. From an epidemiological point of view, surely there is no doubt now that rickets is a dietetic disease, nor can one doubt it from the results obtained by altering the diet. That rickets may be a complicated problem, and that Dr. Mellanby has not finished his work, are obvious facts.

I would like to emphasize the warning which was uttered by Dr. Mellanby, and by Professor Paton too, that you must not apply quantitatively results obtained in the case of one kind of animal to other kinds of animals, or even to the same kind of animal of a different age. The danger of doing so will be seen from certain facts which I shall bring before you as regards the antiscorbutic factor.

What is wanted in this vitamine business is to put the matter upon a quantitative basis. That is more or less impossible at present for rickets—knowledge has not advanced far enough. It is most desirable, however, as regards the other accessory food factors, the action of which is more precisely known. Until such a quantitative basis is reached, not only shall we differ in matters of general principle—as to whether the growth factor is or is not present in one thing or in another, or whether it is or is not destroyed by heat—but it will be impossible to ascertain the minimal quantities required for even one kind of animal. Further, quantitative information is essential to determine the content of these accessory food factors in different food stuffs, and to apply our knowledge intelligently for therapeutic purposes to human beings.

For many years at the Lister Institute, beginning in 1907, many of my colleagues, and other workers there (Cooper, Chick, Funk, Harden, Zilva, Hume, Delf and others), have been striving to place the subject

upon a quantitative basis as regards the water-soluble vitamines, lack of which causes beri-beri and scurvy. Unfortunately you cannot estimate these properties other than by laborious experiments on animals, experiments which last from three to six months. When you ask a question and want to know the answer before proceeding the next step, and you have to wait weeks or months for it, it is a tedious matter. This kind of work needs people of very high character, and although, in 1907, I began to work at the subject of beri-beri, I was soon glad to pass it on to Messrs. Funk and Cooper, at that time working in my laboratory, well recognizing my unsuitability for work making such demands.

I will just bring before you now what have been the results obtained as regards the minimum requirements of the antiscorbutic accessory factor for different kinds of animals, and as to the amount of antiscorbutic vitamine in some common foodstuffs. If I write the figures on the board they will serve as a text.

Not being able to separate this vitamine in a pure form, it is necessary to find a substance which is fairly uniform and contains roughly the same amount as a unit. Lemon juice has been adopted by Dr. Chick for scurvy. We will express it in cubic centimetres per kilo weight of the animal. For rats the amount is negligible. Dr. Harden and Dr. Zilva have reared rats without antiscorbutic substance, and they have bred, and the two generations together have existed over a year and are in very good health, and the only noticeable deficiency in the second generation was, that they would not breed with one another. On the other hand, in the case of the guinea-pig, the amount required per day is as much as 4·5 c.c. per kilo, and for the monkey 0·6 per kilo.

With regard to man, what shall we say? The evidence of clinicians appears to be that something like 1 dr. per day for a child 6 months old is not more than a minimum. Dr. Still tells me he encounters cases of infantile scurvy which have had much larger quantities than that. But if it were 1 dr. per day, that would come out at 0·64 per kilo as a minimum, which makes it very similar to that for the monkey. The amount required by rats is so small that if one were working with these animals one would conclude there was no such thing as an antiscorbutic vitamine, and that indeed was the conclusion come to by McCollum.

Having, by working quantitatively, arrived at the minimum require-

ment of one species of animal, it is possible to evaluate various foodstuffs, and this for practical purposes is very important. That has been done by Dr. Chick and her comrades, and a summary of their various results was published by her in the *Wiener klinische Wochenschrift* in December last, for the benefit of the profession in Vienna. Dr. Chick took lemon juice as a unit, and called the value of 1 grm. of it 100. Cabbage juice and orange juice are about equal, and also 100. Swede juice is good, being represented by 60 on this scale. Green French beans have the value 30. Then we drop away. The carrot, beetroot, beef juice, and lightly cooked potatoes are about the same, with a value of 7·5. Fresh milk is about 1 to 1·5.

The experimental error is rather large—50 per cent. plus—or minus—largely owing to idiosyncrasy in the animals. Nevertheless the results have taken years to obtain. In the same way, having attained a quantitative basis, the effect of the treatment which the food commonly undergoes before consumption, the most obvious of which are heating and preserving, has been ascertained by Dr. Chick, Miss Hume and Miss Delf and Dr. Tozer. If food is heated long enough, all the antiscorbutic property disappears. In some cases it disappears much more readily than in others. In the case of such foods as milk, potatoes, and cabbage the deterioration in antiscorbutic value has been quantitatively shown by Miss Hume, and by Miss Delf and their colleagues, as also in the case of acid fruits and fruit juices, which turn out to be much more resistant to heat. Surely these facts must be of use when you come to deal with your little patients.

Dr. Barton.

I wish to show you this afternoon two substances which I have found of very considerable value at University College Hospital. During the war, when the air raids, combined with deficient food, put nursing mothers off their milk, and hundreds of breast-fed infants in the district had to be artificially fed, we were hard put to it, without milk often, and cream always, to feed the multitude. The best substitute I found was dried milk, and infants made weight on it better than they did on anything else. Still, one felt it was a devitaminized diet, and in view of the investigations at the Lister Institute, it was clear we were not doing our duty to these infants unless we added what was lacking.

Therefore I went down to see Miss Chick on the subject, and she suggested I should use an orange juice in which the rind was minced with the pulp, thereby adding to the juice the preservative effect of the essential oil of orange present only in the rind. She showed me a specimen of such juice many months old, but this contained an amount of the pulp undesirable in the feeds of very young infants. In hot weather I could not get the juice to keep sound over a fortnight. This juice did well, and never disagreed, but a time came when oranges were scarce and juiceless, and I had the temerity to try juices expressed from fresh vegetables, notably lettuce, but my experience leads me not to recommend them. The juices of fresh vegetables seem to be a potent culture medium for every kind of organism, and they smelt badly after a day or two, and as diarrhœa seemed to be caused by such juice I quickly abandoned it. If anyone could give us an efficient preservative for fresh vegetable or fruit juices we should be very grateful.

The other substance I wish to bring to your notice is a cream. When cream could not be obtained the need for something of the kind became urgent. For a year I used Marylebone cream, but felt again that, in view of Dr. Mellanby's researches, the addition of fat-soluble A was wise. Marylebone cream, being composed of linseed oil, contains practically none. I therefore asked Mr. Hampshire to devise a cream of beef-suet, and here it is. I have used it for the last eighteen months, and it answers well. The difficulty in making suet into an emulsion lay in its high melting point, but by the addition of 2 per cent: olive oil we managed it, and you will see some under the microscope. The percentage of suet in the cream is 25, about that of skimmed cream ; it keeps for months, is free of tubercle, and is quite palatable ; it is not expensive, and is made commercially as " University cream."

Dr. Eric Pritchard.

I have a rival cream to Dr. Barton's, and I would like to hand it round for examination. He mentioned Marylebone cream, which I introduced many years ago, and used for some time in combination with separated dry milk. Infants fed for six months on this food did not do very well, so I tried a different sort of fat. I thought I had not succeeded with this cream because it was made with linseed oil and did

not contain the same neutral fats and in the same proportion as exist in breast milk. I therefore asked our dispenser to make a formula which should contain the various fats in exactly the same proportion as exist in breast milk; with this modified Marylebone cream I was highly successful. One of the fats used in this cream was Hugon's suet. We have now obtained a still better cream, in which all the fats are in the same proportion as in human butter fat. It should contain also a large percentage of the fat-soluble vitamine, since it is made from fat which is reputed to contain the largest amount—except, perhaps, cod-liver oil—of any known fat, namely, the depot fat round the kidney of the ox, commercially known as oleo-fat. It is at present difficult to procure, as it is largely used for margarine. This fat from around the kidneys is submitted to hydraulic pressure at a temperature of 120° F., an operation which squeezes out most of the stearin, which is used for the manufacture of soap. The remainder, which is a fairly liquid fat at low temperatures, is highly charged with the fat-soluble vitamine. To bring this mixture to a proper composition, it is mixed with various other oils, chiefly nut oil.

Referring to some of the more general points in this discussion, I feel, with Dr. Hutchison, that we need not fear lest these views are not taken seriously enough: the danger rather is that some will take them too seriously. I have evidence on all hands that the lay public is beginning to think that rickets can be cured or prevented by a teaspoonful of cod-liver oil. My experience of rickets dates a long time back. The first cases I examined critically were those in which, so far from there being a deficiency of butter fat, the latter was used in great excess. Rickets I regard as one of the terminal results of bad feeding, resulting in defective nutrition, and I think there is real danger in attaching the term "antirachitic" to any particular vitamine. It tends to obscure the real pathology. It arises from many causes, chiefly from food causes, but not entirely so. I think the great value of this meeting will be that it will give clinicians an opportunity of explaining their difficulties to the experimental pathologists, and asking for their help in particular directions; we are not in a position ourselves to experiment on our patients and thus elucidate the difficulties of the problem for ourselves. I attach very great importance to these accessory food bodies, and the more we learn about them from experimental work, and the more we apply knowledge thus gained to our patients, the better will be our results. My results have been much better since I have

known more about the special properties of the accessory factors. We want to know, however, what are the particular symptoms of malnutrition which follow the deprivation of these accessory factors. For my part, however, I believe that the majority of the cases of malnutrition with which we have to deal are due not to deficiency, but to excess of some element or elements of food, and there may be symptoms due both to the one and to the other.

I would like to know, for instance, what are the symptoms of malnutrition due to the following dietetic errors: those due to excess of any or all elements, those due to deficiency of any or all, and those in which there is a combination of the two defects. The term "scurvy rickets," which I think originated at University College Hospital, still survives, as if scurvy rickets was a definite disease entirely. There are curious cases—now less common than they were—due to want not alone of the antiscorbutic factor, but due to want of the antineuritic factor as well. Those are the cases, *par excellence*, which have been fed on Allenbury's foods. In such cases there is a mixture of symptoms, due to the want of both the antiscorbutic and the antineuritic factor. They are cases of fat children, showing, more or less, general non-pitting œdema, and in them there is as a rule a marked pseudo-paralysis.

I think also we occasionally meet with another group, due to want of the fat-soluble factor affecting the growth and the susceptibility of the child to infectious disease. Many of the cases of rickets and deficiency disease are complicated by infections, and I think it is infection which may explain the cases Professor Noël Paton referred to, in which the animals could not recover until they were removed to new kennels.

Dr. W. M. Feldman.

I have listened with very great interest to all the speeches and have felt particularly interested in the work of Professor Noël Paton. He attributes rickets to confinement in a close atmosphere. My own clinical observations have shown that confinment *alone* will not produce it, because one finds some children in poor neighbourhoods who are closely confined to the house and yet do not get rickets. On the other hand, I have seen cases of rickets in some children of well-to-do parents, who were brought up on the most hygienic principles as regards air, food and exercise. These facts are not only against Professor Noël Paton's

theory but are also not in accordance with Dr. Mellanby's vitamine theory. It appears to me that amongst the various factors which combine to produce rickets some regard must be paid to the hereditary element. In those children of good families who showed signs of rickets I found some evidence of past rickets in one or other of the parents.

Dr. Lawson Dick.

I wish to join other speakers in complimenting the openers on the way in which they have brought this subject before us. One or two points make it difficult to accept absence of fat-soluble A as the essential cause of rickets. In the East End of London in the L.C.C. schools and dealing chiefly with Jewish children, it was found that: 81·4 per cent. of mothers suckled their children, whilst 18·6 per cent. used cows' milk.

Jewish mothers seldom use condensed milk or artificial foods. The feeding of these infants was excellent, yet 80 per cent. up to 12 years of age presented definite signs of having suffered from rickets. These facts were brought before the Society by me some time ago in speaking of the teeth in rickets. Those who know the state of nutrition of Jewish mothers are aware that they make excellent mothers—their general health is good and their fat nutrition is excellent. Prolonged lactation is blamed in these mothers. In China and India and the East generally prolonged lactation is the rule. Mothers frequently suckle their children for two or three years, even continuing during pregnancy until two children are being suckled at the same time, yet rickets never results.

Another point brought out is the absence of fat-soluble A from lard or at least its great deficiency. If fat-soluble A is so important to the nutrition of the child this is a somewhat peculiar result. Clinically, bacon fat is an excellent way of giving fat to the very young child.

Again, rickety children by no means always suffer from malnutrition. Frequently they are very fat, especially when fed on sweetened condensed milk. The child may be so fat that it is difficult to feel the ribs or the epiphyses of the long bones and yet the child is distinctly rickety.

There is the geographical aspect. We ought to look at rickets from a much wider survey. From 40° to 58° N.—say from the middle of Italy to the North of Scotland, and extending across Europe and

America—will include the whole belt in which rickets is rife. It is a temperate zone, a zone of deciduous trees, and a wheat bearing zone. But, above all, it is a great industrial zone, the great industrial zone of the world. It is the zone of great cities and dense populations. Only in China perhaps, is there anything to compare with it in this respect, and there it is a rice-fed population. It appears to me that vitamines have not been proved to be a serious factor in producing disease in this country. We live in the wealthiest portion of the world, where the people live on the most varied diet, and yet we find these deficient factors in food blamed for causing rickets. It is, I should imagine, very difficult to exclude a sufficient quantity of vitamines. from any child's diet in this country. In China and Japan it is different. Professor Castellani, in his book on tropical diseases, says 400 millions of Malays, Chinese and Indians, live on rice, and there you have the ideal conditions favouring diseases due to deficient vitamines, and so, on this view, you would expect to find those diseases. Yet in these countries for all practical purposes rickets is never seen. The question of the occurrence of rickets in dogs is a very difficult one. They are prone to rickets. Stoeltzner pointed out long ago the tendency they show to pseudo-rachitic osteitis. I have had the opportunity of seeing some of the specimens of Dr. Mellanby, and they are most excellent. I am sure this work is well worth pursuing. The teeth changes produced are different in dogs to what we see in children: there is an expanded cavity in Mrs. Mellanby's cases, and no enamel, quite different from the hypoplastic type seen in young children, in whom the dentine is very dense; it is remarkable how well these hypoplastic teeth frequently last.

Dr. Mellanby (in reply).

Most of the speakers would apparently be whole-hearted believers in the importance of accessory food factors in child nutrition were it not that they are blessed with the name "vitamines." The word "vitamine" is unfortunate, and it may not be satisfactory to all to speak of the "antirachitic accessory factor," but I have worked at rickets for some time and, for my purpose, at any rate, it suits. We must give a name to the substances, and the great need is to get the facts linked up. It is useless to tell us to take broader views; when we take broad views,

we never seem to get to the point. Rickets is a disease whose source we can elucidate, and although it is necessary to start an investigation with broad views, the experimental method allows us to eliminate one factor after another until we can get the issue narrowed down to the closest limits. The subject is of tremendous importance and does not end with rickets, because in these cases the whole vitality of the child is lowered and it may succumb to one of many diseases. One speaker mentioned non-resistance to infection. There is no doubt that this is a fact and the low resistance of my puppies to infection has always been a source of great trouble. Three weeks ago, I got an outbreak of distemper and, as a matter of experience, I knew it was of little use continuing a comparative investigation with them, so in a few days the whole lot were killed and a fresh beginning made.

Dr. Lawson Dick said in the discussion that the dogs' teeth in my wife's work, which he has had the opportunity of seeing, are not comparable with those of children seen in the East End schools. That is a matter of opinion. Some medical men and dentists have expressed the view that the teeth changes are comparable in the two cases. Naturally, because of the necessity of producing rapid results, the diets of the dogs are often so deficient as to produce results more exaggerated than are met with in children.

The most emphatic criticism which we have heard in this discussion has been that of Professor Noël Paton. It is surprising how unanimous speakers have been in regarding these vitamines of importance and how closely the animal and clinical results have agreed. Professor Paton is hardly prepared to admit there are such things, and, in any case, he thinks we are making far too much of them. On behalf of those who are working in the laboratory on the subject, I disclaim any blame for people taking this excessive view of things. That has been largely due to the subject having been written up in the press, and those who have done it have not always properly followed what we have said and have often given their imagination too much licence. The laboratory worker has, on the whole, been careful in making claims, and has usually done so with a full sense of responsibility. In the opening remarks of this discussion, I spent most of the time dealing with the relation of the antirachitic factor to the other elements of the diet, and I think this is probably the first time this relationship has thus been emphasized. That people write extravagantly about vitamines is not our fault.

So far as I could follow, Dr. Hutchison's remarks as regards children agreed very well with what I said about rickets in puppies. He took the attitude of the canny Scot, but agreed with my facts. If the facts are accepted, I can conceive of no other course than the whole-hearted acceptance of the vitamine hypothesis.

It is difficult for me to say anything about Professor Paton's criticism. He is a member of the Medical Research Committee, for which body all this work has been carried out. Anyone can see my work at any time. It is only a question of asking me and I shall be glad to go over the results with anybody who wishes it. It would be much easier and more satisfactory for a member of the Medical Research Committee to examine my results at close hand than to come here and condemn my work by saying I have produced insufficient evidence. My research on rickets has lasted about five years, the last three of which I have concentrated on the vitamine hypothesis. I was led to this explanation solely by my experimental results and against my inclinations. That the results have not been published in full means that the problem has not yet been solved; what has been published simply indicates the type of work being done at the time and the trend of the results. It has given the opportunity to other workers to join in, repeat and extend the work.

Professor Paton made a great deal of the fact that in my lectures on rickets, in 1918, I did not take the dogs in families. According to him, only comparable results on dogs of the same families are of any value. I have, as a matter of fact, made many comparative experiments on families, but the problem to be solved is not one of rickets in families but rickets all over the country. It would be easier to work on dogs of the same breed and age, but that condition I have not been able to secure. I have had to work on any puppy I could get hold of. Moreover, if the problem can be solved with dogs of different families and breeds and all the facts made to fit it, the work will obviously be the more convincing.

Professor Paton also criticized me for having pointed out that several of Findlay's dogs died during the experiment, whereas I did not mention how many of my own died. Findlay set out to prove and claimed to have proved that rickets is due to lack of exercise. Therefore, I think he should have taken the precaution to see that his puppies had a perfect diet. If some of his animals died, it is evidence to me that they did not have a perfect diet. My animals die, especially if any infection

gains access to the kennels, because the majority get an unbalanced diet. Therefore he misses the whole point of my criticism, because all my results point to diet being the prime cause of illness and death in early life.

If we assume, as has been suggested, that the hereditary element explains the occurrence of rickets, we shall become involved in a hopeless kind of problem. I do not mean that heredity has nothing to do with its occurrence, but I shall only fall back on that hypothesis when all other means have failed. Some animals are more susceptible to lack of vitamine than are others, but I suggest to you that this is largely due to the variability in rate of their growth and metabolism of the animals.